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Long Term Consequences of Illicit Drug Use During Pregnancy

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Introduction

Illegal substance abuse is a growing problem, especially in young adults, including women of childbearing age. Therefore, knowledge of the effects of drug abuse during pregnancy is important, in order to correctly counsel the parents and to know how to manage the newborn baby. For evident reasons knowledge on this particular problem relies on animal experiments and reports on human observations. In this manuscript we describe the long term outcome of children after intra-uterine exposure to illegal substances.

Marihuana is the most widely used drug in the Western world and the favorite drug used during pregnancy. In 1964 Gaoui and Mechoulam found tetrahydrocannabinol (THC) to be the most psycho-active substance in marihuana. In 1988 Devane et al confirmed the presence of an endocannabinoid system in the human body. Cannabinoid receptors are present in several tissues: brain, placenta, uterus, ovaria, and in the foetus. Among others, endocannabinoids play an important role in the progression of pregnancy and in the plasticity of cerebral synapses. Exogenous THC binds to the receptors longer than the natural endocannabinoids, thereby causing pathophysiological changes. Tetrahydrocannabinol crosses the placental barrier and is detectable in the blood of the foetus. As far as we know, THC is not teratogenic [1]. After intra-uterine exposure to THC, the risk of sudden infant death syndrome (SIDS) is raised. Tetrahydrocannabinol is secreted into breast milk and ingested by the baby. Prolonged exposure to THC by breast feeding may influence neuromotor development of the baby. From the age of 3 years on, children may suffer from cognitive disorders (short term memory, verbal reasoning, concentration deficits, abstract thinking) and behavioural problems (hyperactivity, impulsivity, more criminal behaviour), that persist into adulthood [2]. As early as at the age of 10 years, symptoms of depression may emerge, evolving towards a full-blown clinical psychiatric picture. Epidemiologic studies suggest a relationship between intra-uterine exposure to marihuana and the development of acute non-lymphoblastic leukemia at child age. Adolescents who have been exposed to THC antenatally are at higher risk of addiction to nicotine and marihuana. Exposure of the developing foetal brain to THC causes a rise in the number of cannabinoid receptors in the brain, making the adult brain more susceptible to the addictive effect. Genetic and environmental factors may play a role as well.

The main substance in an ecstasy tablet is 3,4-methylenedioxymetamphetamine (MDMA). A single exposure during pregnancy without maternal toxicity is not teratogenic [3]. In cases of repeated antenatal exposure, more cardiovascular defects (ventricular and/or atrial septal defects), musculoskeletal abnormalities (clumb feet), prematurity, low birth-weight and small for gestational age babies [4]. Experiments in rats indicate a higher risk of long term disturbances in learning capacities and memory after 3rd trimester exposure [5]. The 'Drugs and Infancy Study' found that babies from young mothers who used MDMA during the 1st trimester of pregnancy showed a severely delayed psychomotor development [6].

As far as we know the use of opioids during pregnancy has no teratogenic effect [7]. The risk of SIDS is raised times 4 to 5. The long term consequences for the child are presumably determined by socio-economic factors. Antenatal exposure to opiates in animals reduces cortical neuronal density and dendritic and axonal ramifications. The significance in humans of these findings is not clear. There is a higher risk of delayed psychomotor development and behavioural disturbances during the first years of life.

Cocaine is a neuro-excitatory substance that causes abnormal behaviour with tremor, dystonic movements, irritability, abnormal sleeping pattern, poor feeding (newborns may need gavage feeding for days or weeks), vomiting, diarrhoea, fever, sneezing, high pitched cry, extreme sucking reflex, hyperactive Moro reflex, tachypnea, hypertonia, rarely convulsions [8-10]. The clinical picture is caused by a direct neuro-excitatory effect rather than abstinence. Cocaine use during pregnancy has been associated with prematurity, intra-uterine growth retardation (IUGR), microcephaly and a spectrum of abnormalities, caused by vascular dysruption sequence

[8,11]. A higher incidence (6,5 %) of cardiovascular anomalies has been reported, such as peripheral pulmonary stenosis, patent ductus arteriosus, ventricular and atrial septal defects. Transient ST-segment elevation on electrocardiogram (ECG), marker of transient myocardial ischemia, has been documented. Children who have been exposed to cocaine antenatally are at higher risk of necrotising enterocolitis, with rather late onset of disease [12]. Breast feeding is prohibited: ingestion of cocaine with the mother's milk carries the risk of acute intoxication, manifested by vomiting, diarrhoea, irritability and hypertension [13]. Information in literature on the long term consequences of antenatal exposure to cocaine is inconsistent. Children with microcephaly at birth do not show catch up growth of their head circumference at 2 years of age and suffer from psychomotor retardation. Reports on cognitive-, motor-, speach- and behavioural development give inconsistent information [9]. Boys would be more prone to motor sequelae than girls. Some authors found a dose-respons effect. A prospective study in 219 children, followed from the 4th month of gestation, did not find any problems with global cognitive development, learning capacities or memory at age 15 years [14]. However, first trimester prenatal exposure to cocaine was significantly related to delinquent behaviour, reduced problem solving capacities and abstract reasoning. At age 15 years, children had a lower body weight, shorter stature and smaller head circumference.

We found only 1 case report on the use of 'liquid ecstasy' (gammahydroxybutiric acid) during pregnancy [15]. Long term outcome is not described. The same accounts for lysergenic acid diethylamide [16].

Neonatal abstinence syndrome (NAS) is present in 60-80 % of babies whose mother used methadone and usually starts on day of life 3, but may ensue after 4 weeks as well [17]. Hyperphagia (> 190 to 290 mL/kg/day) is a marker of higher metabolic demands during NAS and is not associated with more weight gain or gastro-intestinal disturbances [18]. On the contrary, there is higher risk for excessive weight loss, especially in breast-fed children [19]. It takes more time for babies to regain their birth-weight. Methadone intake is a well known cause of long QT in adults. Clinically significant long QT in a neonate after antenatal exposure to methadone has been described [20]. Bradycardia or irregular heart rythm in a neonate whose mother took methadone during pregnancy has to be taken seriously and documented by an ECG. Flash visual evoked potentials may be abnormal in the 1st 2 weeks of life [21]. Concomitant use of benzodiazepines might contribute to that finding. It is not yet clear whether these changes are transient effecs of methadone and/or other substances still circulating in the blood of the newborn, or the consequence of a teratogenic exposure with long term consequences for visual function. Breast-feeding is allowed, even with higher doses (> 40 mg/day) of methadone [22]. The quantity of methadon ingested by the neonate will not suffice to prevent the NAS, but there are indications that the course might be more mild [19]. Long term consequences are probably determined by socio-economical factors. Although birth-weight is usually regained at a later time, further growth is usually not problematic.

Buprenorphine is a semi-synthetic thebaïne derivative, that is inceasingly used instead of methadone for treatment of opioid dependent pregnant women [23]. Neonatal abstinence syndrome occurs in more than 50% of cases, but is usually rather mild [24-26]. There is no relationship between maternal dose and the severity of NAS. Treatment is not always indicated and, if necessary, morphine is administered. Buprenorphine is secreted in breast milk, probably only in small amounts . Breast feeding is allowed as it may diminish the need for treatment of NAS. Prenatal exposure to buprenorphine raises the risk of SIDS, probably only in cases of suboptimally treated NAS [23].

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